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SUMMARY

The 2018 annual report is the last report covering a full year in the SLRC and the journey as an SFI will end at 31st of August 2019. The Research Council came for a site visit in October 2018 and a summary of the achievements was presented in relation to the aims and goals given for the SLRC in the project description. The summary showed that all except one goal were completed one year ahead of the SLRC date of closure. The unfinished goal is the IPM work that was decided to be terminated by the board due to large changes in lice management by the industry. There are still a number of trials and projects to finalize within the centre and the processes started in the fall 2018 and will continue in 2019.

The principal investigators in the SLRC will present the scientific work in the centre later in this report.

In 2018, the board and management have had a special focus on work related to a continuation for the SLRC after the period as a SFI has ended. The SLRC has had an extensive process on this topic and “exit” has been discussed among centre members, WP-leaders, with the SAB and with both academic and industrial partners. Furthermore, a working group was appointed by the board to develop a future centre structure – partners, activity, organisation and funding. The working group ended up with a model with the farming industry as core partners together with the academic partners. In the fall 2018, the board at UiB decided to support and provide funding and host a future SLRC, and IMR committed similar support. The aim is to develop and continue with a centre that has approximately the same annual core budget as the current SFI. The planned centre will have a basic funding from academic partners and farming industry (50:50) and have a strengthened focus on biological prophylactics (vaccine work and host resistance). There are still a few uncertainties whether we will succeed in establishing a continuation of the SLRC, but Lerøy Seafood Group ASA has taken a lead among the large farming companies and with their support and help, I hope the future is secured.

Frank Nilsen
Director SLRC
Sea lice (*Lepeophtheirus salmonis* and *Caligus* spp.) are the major pathogens affecting the global salmon farming industry and have a significant impact in many regions. The annual loss has recently been estimated to €300 million and the aquaculture industry relies heavily on a few medicines for lice control. Widespread resistance to these medicines has increased the need to develop new treatment methods (biological, prophylactic and new medicines) and tools to avoid increased losses due to sea lice and to ensure a sustainable salmon farming industry in the future.

Research conducted at the centre will focus on methods and tools to facilitate the development of new medicines, develop new tools for resistance monitoring, reduce attachment in infective stages, improve host response to infection, identification and evaluation of new targets for a future sea lice vaccine, and to explore the possibilities to utilize RNAi as a novel method in lice control. By using the salmon louse genome sequence as a starting point, functional genomics methods will be utilized to identify molecular markers for drug resistance to facilitate monitoring and prolong the life time for valuable anti sea lice drugs. The Sea Lice Research Centre (SLRC) consists of the leading scientists within the field together with the major industrial players, represents a strong consortium to develop short and long term solutions for one of the most significant problems for the salmon farming industry world-wide. This will be achieved through state of the art research in relevant fields (parasitology, molecular biology and genomics, pharmacology, host parasite interactions) and establishment of an integrated database resource for the salmon louse genome in addition to state of the art wet-lab facilities for sea lice research. Results from the SLRC will enable an integrated control system to be established, based on key features in sea lice biology, to improve sustainability of the salmon farming industry.
The SLRC Chairman’s comments – yearly report 2018

Investment in SLRC gives high return

The last year has been marked by intensified passion, energy and workload. The centre’s skilled researchers and technicians have ensured that all by one of the goals for the lifespan of the SLRC are achieved ahead of plan – congrats to you all! The management juggles even more tasks than before, making sure that the centre is terminated as an SFI in the best possible manner in parallel with the preparations for its afterlife. The Board endeavours are focused on securing the financing of the centre’s future, as well as fulfilling all formal requirements and responsibilities. A busy year – and more to come!

All but one goals achieved – and still we hear statements like “the centre has not delivered as expected”. “Expectation management” is challenging. It is indisputable that the performed research and the results obtained has brought unprecedent knowledge on sea lice. Frank Nilsen and the WP leaders describes this further in the scientific part of this yearly report. Read and enjoy.

Throughout the last year, the Board has proactively worked towards securing a continuation of the centre. We were thrilled to learn about the dedication UiB demonstrated by its clear commitment to include the SLRC as a special unit within its marine focus. HI followed with its assurance of continued contribution at the current level or above. These two dedicated high-quality academic partners form the basis of the continued centre, SLRC2. Their contribution depends on a regulatory requirement of obtaining matching industry support. We are more than pleased that Lerøy Seafood is committed to contribute and look forward to welcoming other fish farming companies in this common effort to combat the sea lice. The centre is dependant upon predictable funding for a 5+5 years period to proceed the research and maintain the infrastructure.

A Task Force was established with the aim to define the strategic basis for a continued centre with regard to science, organisation and funding. Sustainable sea lice control needs to be anchored in preventing infection, with treatment of established infestation as the exception, not the rule. SLRC is in the best position to drive this development. Resistance against sea lice in Atlantic salmon may be achieved by vaccination or genetic resistance. Both methods may be revolutionary in the fight against sea lice, and secure a more environmentally friendly, sustainable and effective parasite control. By using new technology already established in the centre, like CRISPR, we may evaluate candidate genes responsible for turning on resistance.
Sea lice is the main challenge for the salmon farming companies. The cost involved in treatment are high, there are fish health and welfare challenges with current mechanical methods and sea lice on wild salmon is the only indicator for allowing growth according the new “traffic light” regulation.

Investing in continued development of preventive measures could give high payback - not only by reducing costs, but also by increased fish welfare, sustainability, growth opportunities and public opinion of the fish farming industry.

Last but definitely not least, I would like to present the Board’s sincere thanks to all the researchers and technicians who are steadily striving throughout the last months of the centre, even in times of insecurity for the future. The partners will match this commitment in carrying out their obligations according to the consortium agreement bringing the centre eloquently to its end as an SFI. There is still much work awaiting us all before we will gather to celebrate at the SLRC symposium early fall!

Oslo/Bergen, 20. March 2019

Benedicte H. Fossum
Chairman of the Board
CENTRE VISION AND GOALS

The SLRC aims to be the world leader for research on the salmon louse and similar parasites. The nature of the centre will facilitate development of new methods for lice control and shorten the time from basic research to new products and tools for parasite control in the aquaculture sector to achieve a true integrated pest management in the future.

SLRC objectives
- New medicines and resistance monitoring & control methods (WP1)
- Anti-attachment diets (WP2)
- Immune controls (specific & nonspecific) (WP3, WP4)
- RNAi gene techniques for research tool development and future controls (WP4)
- In depth knowledge of the molecular biology of growth, reproduction and endocrine systems in sea lice (WP4)
- Annotated genome sequence linked into an integrated database containing experimental data (WP5, LiceBase)
- Updated microarray and other molecular tools (WP3, 4, and 5)
- Larval detection and assessment techniques (WP4)
- Sea lice facility (naïve lice population, challenge facility, etc.) (WP6, LiceLab)
- Development of true integrated pest management techniques for industry (Part V)

ORGANISATION

The SLRC’s academic and industrial partners have diversified location, with the main scientific activity in the centre located both in Bergen and Oslo. People working for the SLRC at IMR and UiB are co-located in the SLRC facilities at the host institution UiB at Marineholmen.

The industrial partners are complementary to each other being linked together by the academic partners. The eight SLRC partners in 2018 are presented below.

University of Bergen (UiB) is the host institution for the SLRC. Senior scientists from three departments at the faculty of mathematics and natural sciences are the base for the research in the SLRC. Senior scientists within biology, molecular biology and bioinformatics use their knowledge in the SLRC. The main wet-lab activities take place at UiB, where lice strains are kept. PhDs and Postdocs are educated within the center.
The Norwegian University of Life Sciences (NMBU) is represented in the SLRC with senior researchers from the Department of Food Safety and Infection Biology and the Department of Basic Sciences and Aquatic Medicine. PhDs and Postdocs are hired to work with the research in the SLRC. This partner is responsible for WP1 and WP3 and has close connections to WP2 and WP4. Until now, the main cooperating partners have been PatoGen Analyse, Elanco, EWOS and UiB.

Institute of Marine Research is represented in the SLRC with one senior researcher (80%), 1 post doc, 1 PhD student and one wet lab technician (50%). Major wet-lab activities, mainly RNAi trial takes place in the laboratories in Bergen. The Post doc and the PhD work in WP4, whereas the researcher works in both WP4 and WP6, where the technician also is connected.

Cargill is one of the world’s largest privately held companies and with the acquisition of EWOS in 2015 they became a global leader in aqua nutrition. Cargill’s animal feed business is divided onto three business segments; Cargill Feed and Nutrition, Cargill Premix & Nutrition and Cargill Aqua Nutrition. Cargill Aqua Nutrition develops and produces feed and feed solutions for three key species – salmon, tilapia and shrimp – in 18 countries around the world. In addition to this, Cargill Aqua Nutrition also consist of Innovation centers and Technology application centers. EWOS Innovation AS is a user Partner in the SLRC with a long history of sea lice research. Scientists are based in Bergen, Dirdal, and Colaco in Chile, where research facilities have been expanded the last years. In the SLRC, development of compounds that reduce the settlement and survival of lice will be the focus. EWOS Innovation is the leader of WP2 and is involved in several of the projects in the other WPs.

Lerøy Seafood Group ASA is one of the world leading salmon farming companies with more than 100 farming licenses in Norway, in addition to slaughterhouses and processing factories. In the SLRC, the company is a supplier of raw materials and facilities for field trials. Lerøy has also been an important contributor in the field validation of the novel analyses of the diagnostic PCR-analyses for resistance monitoring developed by PatoGen. First-hand information on needs and demands from the industry gives Lerøy an important role in the SLRC.

PatoGen AS is a biotechnology company that develops and sells gene technology analyses that are used to reduce disease related loss in the aquaculture industry. PatoGen has the most modern laboratories for Real-Time PCR analyses for detecting fish pathogens in Norway, and work in close collaboration with research partners and industrial partners in the SLRC. PatoGen is mainly involved in WP1 and WP4, and collaborate with the partners UiB, NMBU, Marine Harvest ASA, Lerøy Seafood Group ASA and Elanco Animal Health.
Elanco Animal Health Formerly Novartis Animal Health AG. The Animal Health business of Novartis was acquired by Eli Lilly & Company in January 2015. Elanco Aqua Business develops and commercializes leading technology and innovative vaccines and pharmaceuticals to meet the needs of salmon farmers and veterinarians. Elanco’s R&D and Global Technical Services functions located in Norway, Canada, US, Australia and Switzerland take part in different WPs and adjacent collaborations with the other partners in the SLRC.

Marine Harvest ASA is a world leading Seafood Company and is present in all major salmon farming regions. The knowledge and international network which Marine Harvest brings is clearly an added value for the centre. Marine Harvest has been an important contributor in the field validation of the novel diagnostic PCR-analyses for resistance monitoring, developed by PatoGen AS. In addition, Marine Harvest is a supplier of raw materials and facilities for field trials in the SLRC.

Management

UiB being the host for the SLRC, is responsible for the coordination of all activities in the centre. The Centre Director Frank Nilsen and the administrative coordinator Ingunn Wergeland carry out the day-to-day management. The overall decision-making body is the SLRC board, where all the partners have one representative each. There have not been any changes in the Board during 2018. The Board is chaired by Benedicte Fossum, an independent chair elected by the partners of the centre.

SLRC Board Members in 2018:
- Bjarne Reinert, Lerøy Seafood Group ASA
- Trude Hagland, EWOS Innovation AS
- Jose Fernando Rodrigues, Elanco Animal Health
- Gordon Ritchie, Marine Harvest ASA
- Vidar Aspehaug, PatoGen AS
- Karin Kroon Boxaspen, Institute of Marine Research
- Amund Måge, University of Bergen
- Ole Taugbol, Norwegian University of Life Sciences
- Benedicte Fossum – Chair of the board
The Board decides the strategy, annual work plans, activities, budget and the organisation. The Exit Strategy for the SLRC has been a major task for the Board in 2018. The partners would like the activity in the centre to continue in a new organisation, and a task force was established from January 2018 to speed up the process. The task force has developed a strategic scientific plan for phase 2 of the SLRC and various models for organisation and funding. Plans and progress have been presented for the Board throughout the year. Valuable discussions on how to achieve the goal to continue the centre with an applied research focus have been essential for arriving at a model all partners support.

**Scientific Advisory Board (SAB)**

For the last period of the centre, three new members have been selected for the SAB. Their main task is guidance to future work based on the SLRC project description, and to give the centre recommendations regarding experiments and new projects. In 2018, all the SAB-members have been of great value in discussions on the future of the centre; both regarding the scientific focus areas and how to organise and fund a future centre without basic funding from the RCN. Participation at the SLRC Workshop in the spring was an important arena for giving input to all the levels of the centre. The SAB is also an important source of information on what is going on in related areas of research and to seek for new possibilities, which is important if the centre will continue in a perspective of 5–10 years.

The members of the SAB are:

- Dr Ian Denholm, Rothamsted Research/University of Hertfordshire
- Professor Chris Secombes, University of Aberdeen
- Professor Kurt Buchmann, University of Copenhagen
SLRC Arrangements and cooperation

One workshop for the centre was arranged in 2018. The SLRC organisation was gathered at Quality Hotel Olavsgaard 30–31 May. The main purpose of the workshop was to update all participants on the research going on in the various parts of the centre and to further develop and identify areas for collaboration between WPs and partners. PhD students and postdocs gave detailed scientific presentations. To share knowledge is an important to enable dynamic work processes in the SLRC and this meeting is also an important facilitator to update partners on scientific progress. Parts of the Workshop was divided in parallel sessions:

• WP-leader meeting, including members from SAB
• Board Meeting
• Working Groups for PhDs, Postdocs and researchers

Research in the different WPs and sub-projects involves all the partners in the centre, and is an important tool to ensure transfer of knowledge to facilitate innovation and development of new products and methodology. Combining the partners’ knowledge and expertise is a key factor to achieve the goals for the SLRC. To gather all levels of the organization provides possibilities for fruitful discussions forming a base for ideas and future collaborations.
SCIENTIFIC ACTIVITIES AND RESULTS

High quality research has its own value and is an important key for innovation and development in the modern world. Salmon farming has developed into a large industry in Norway and is currently one of the most significant export industries for our country. However, this would not be possible without research and development. The bottleneck with bacterial diseases was largely solved through research and development of efficient vaccines that resulted in a large jump in production. Infections with the salmon louse have been present since the first salmon were farmed and currently represents one of the largest production costs. Research from the SLRC has resulted in new products available for the industry and the large amount of new knowledge produced and published will improve how the salmon louse is managed in the future. Research in the SLRC covers important aspects ranging from basic biology, physiology, pharmacology/medicine mode of action, host-parasite interaction/immunology and applications like screening for new active compounds, clinical testing of vaccine candidates and testing and evaluation of feed ingredients. All these fields will provide pieces to the puzzle for how sea lice should be managed and controlled in the future. The results provided in the 2018 annual report clearly show high quality research and scientific publications in what many regard as an applied field.

WP1: Chemotherapy and resistance

Principal Investigator: Tor Einar Horsberg, NMBU

General introduction
The aims of this work package are to 1) explore possible new treatments for salmon lice, and 2) identify mechanisms for resistance / tolerance development in the parasite against various treatments, and to develop high-throughput methods to detect these. The aims interact since resistance development triggers activity to find new control methods, and identification of resistance mechanisms often increase the knowledge about the mechanism of action for a treatment. In 2018, the main research focus has been on identification of compounds interacting with the nicotinergic acetylcholine receptor in salmon lice, the mechanism of action for pyrethroids in the parasite, screening of a series of novel compounds in bioassays, development of molecular assays for identification of resistance towards azamethiphos and hydrogen peroxide in *Lepeophtheirus salmonis* and *Caligus rogercresseyi*, as well as studies on possible tolerance development towards non-medicinal control methods for salmon lice.

Chemotherapy
The nicotinergic acetylcholine receptor is an indirect and direct target for some of the most commonly used chemicals against arthropod infestations worldwide: organophosphates, carbamates, neonicotinoids. The receptor is a ligand-gated ion channel involved in transmission of nerve signals in synapses and neuromuscular junctions, the transmitter being
acetylcholin. In 2016, bioassays with eight compounds in the neonicotinoid class revealed several of these being highly effective against larval and pre-adult stages of *L. salmonis*. In 2017, candidate genes coding for subunits of the receptor and auxiliary proteins were identified in the salmon louse genome ([https://licebase.org](https://licebase.org)) and RACE-PCR was used to obtain the full sequences of the transcripts. In 2018, the transcripts were cloned into a well-described ex-vivo model (*Xenopus* oocytes) and functional channels were generated. Cloning was done by the Swiss company INVENesis Sàrl. Through electrophysiological techniques (patch-clamping), the ex-vivo response of the receptors to eight neonicotinoids, as well as azamethiphos, emamectin benzoate, deltamethrin and cypermethrin were tested. The study resulted in interesting results regarding the stoichiometric organization of the receptor and its response to various compounds. The results are currently processed for publication.

**Figure 1.1:** Dose-response to acetylcholine in eight *L. salmonis* nicotinergic acetylcholine-receptor configurations, expressed in *Xenopus* oocytes

In 2018, 33 novel compounds were screened for efficacy against salmon lice copepodids in bioassays, several showing a high efficacy at low concentrations. Some of the compounds will also be subjected to screening for efficacy on molting (nauplius → copepodid), and some for efficacy on pre-adult parasites. The pre-adult assays will be conducted in Bergen in 2019. The study is conducted in cooperation with Elanco.

Through an associated project, the mode of action and resistance mechanism for pyrethroids (deltamethrin and cypermethrin) in salmon lice has been studied. A strong association between programmed cell-death (apoptosis) and deltamethrin exposure was demonstrated, the association being significantly stronger in parasites from a pyrethroid-sensitive strain. Apoptosis was most prominent in muscle- and subcutaneous tissues. These results point to an energy-inhibiting effect of deltamethrin in salmon lice, which has not been described in arthropods earlier. The results were published in 2018 in Scientific Reports.
Resistance

In 2014, an important mechanism for resistance towards hydrogen peroxide, overexpression of the enzyme catalase, was revealed, and PatoGen developed a molecular Taqman assay for this genetic marker and commercialized it. As the expression of this gene is inducible by several stressors in addition to \( \text{H}_2\text{O}_2 \) treatments, this assay alone was somewhat inaccurate in some cases. In 2017, several other genes were found to correlate in their expression with the elevated expression of catalase in \( \text{H}_2\text{O}_2 \)-resistant parasites. These included genes coding for wound healing factors, factors that improve the ability of the parasites to cope with oxidative stress, and genes coding for transport proteins. Through an associated project one of these genes was further validated as a potential new marker for resistance, both in \( L. \) salmonis and \( C. \) rogercresseyi. Its expression was not altered by stressors. Thus, when used together with the catalase marker, this additional marker was demonstrated to give an excellent prediction of the sensitivity of parasites towards hydrogen peroxide. A patent application has been prepared for this additional marker and the main work will be published.

In 2015, a mutation was found in the gene coding for acetylcholinesterase in the Chilean sea louse, \( Caligus \) rogercresseyi. This mutation occurred in a highly conserved region of the gene and was strongly correlated with resistance towards the organophosphate azamethiphos. The mutation resulted in a change from the amino acid phenylalanine to valine in position 318 of the protein, which resulted in a larger enzymatic gorge and likely altered binding properties of azamethiphos in the gorge. PatoGen developed a high-throughput Taqman assay for the mutation, and the occurrence was validated against bioassay results on samples from several sites in Chile in 2018. The results were published in 2018 and PatoGen will in 2019 commercialize the assay in Chile.
The control of salmon lice in the salmon industry has over the last three years changed from chemotherapeutants to non-medicinal methods like high-speed flushing, fresh water and warm water. None of these methods are 100% effective, and earlier work from the SLRC has demonstrated that lice display genetic variation in sensitivity to both fresh and warm-water treatments. Therefore, there is a risk that the parasites surviving such treatments on commercial farms may cause a shift in the sensitivity to such treatments, as has been the case for medicines. Therefore, bioassays for warm water and fresh water were developed in 2017 and 2018, and a limited number of strains were tested. A variation in the sensitivity for these methods was detected both in copepodids and pre-adults.

**WP2: Anti-attachment**

**Principal Investigator: Stanko Skugor, Cargill Innovation Center/Ewos Innovation AS**

The acquisition of custom made functional ingredients of herbal (phytogenics) and microbial origin continued in 2018. Their screening against two sea lice species was executed at two research facilities of Cargill Innovation Center (CIC), in Norway against *Lepeophtheirus salmonis* and in Chile against *Caligus rogercresseyi*. In addition, novel Cargill anti-parasitic functional feeds were screed in Canada, at the Memorial university of Newfoundland (MUN), and the Atlantic Veterinary College (AVC), as part of activities in the associated IPMC/GAPP2 project which targets co-infection of lice and microbial pathogens (bacterium at MUN and virus at AVC). The pre-screening of functional ingredients by In Vitro methods now takes place only in the facility in Colaco, Chile and relies mainly on LD50 and frontal filament assays. Noteworthy here is that the anti-parasitic research program at
CIC expanded greatly over the last couple of years. The new generation of anti-parasitic feeds at Cargill aims to target not only lice but also other ectoparasitic parasites: amoeba *Neoparamoeba perurans* causing amoebic gill disease (AGD) in Atlantic salmon, and protozoan *Cryptocaryon irritans* causing itch in the marine fish species Golden pompano. This work has significantly expanded our knowledge of phytogenics and their modes of action, which is relevant for the development of anti-attachment functional feeds for Atlantic salmon parasitized by lice. Another line of functional feed research at CIC of relevance for anti-attachment program is the development of Welfare functional feeds. The market landscape for anti-parasitic treatments, including functional feeds has greatly changed in the last few years. In Norway, a shift from chemoterapeutants to increased use of delousing methods that deploy mechanical and thermal treatments which cause stress, inflict wounds on gills and skin, is associated with slower growth and mortalities. To address the compromised welfare of fish during these operations and help faster wound healing, CIC has established thermal and wounding challenge models, which have resulted in the development of the functional feed that accelerated healing of wounds by 40%.

Investigation of molecular mechanisms behind the protective effects of functional feeds continue by profiling gene expression of skin and other involved tissues, and by profiling mucus for the expression of several immune factors. In addition to studying Atlantic salmon’s physiology and immunity during lice challenges and dietary interventions, in 2018 we collected lice samples from a field trial to investigate the effects of functional feeds on the parasite itself.

**In Vitro work**

Prior to investigating the dietary effects of promising new functional ingredients, they are typically first screened for their anti-lice properties by LD50 and frontal filament assays, which are now running in our facility in Colaco, Chile. As our anti-parasitic program has expanded to include amoeba *N. perurans*, we now also screen functional ingredient candidates in amoeba *In Vitro* cultures. We are currently using the polyculture amoeba isolate from Chile; with the goal to better understand general anti-parasitic effects of our phytogenic candidates. Depriving lice of essential nutrients (iron/heme) by manipulating iron metabolism of the host is recently proposed to be one potential way of increasing resistance to parasites. To test phytogenic compounds with potential to modulate iron metabolism, we have developed a cell culture model based on salmon SHK cells accompanied with a gene expression panel to evaluate effects on iron metabolism.

**In Vivo screening of novel feed ingredients**

We have evaluated five phytogenic functional ingredients and one product of microbial origin in Norway in *Lepeophtheirus salmonis* challenge trials, while in Chile, we evaluated one phytogenic product in the *Caligus rogercresseyi* trial. In Norway, we dedicated some tank resources to testing 1) combinations of two phytogenic ingredients, 2) combination of a phytogenic and product of microbial origin, and 3) one product of bacterial origin was tested in the background of two dietary formulations. Skin tissue samples from a trial
which yielded the most prominent reduction of lice numbers in 2018 will be analysed by microarrays during 2019. Control samples, and three dietary test groups will be profiled to learn about the mode of action of the ingredient in question. We are currently assessing another promising candidate in fresh water fish over a longer period of time to learn more about its effect on growth and welfare parameters and if combinations with appetite enhancers can improve these parameters. In Vivo challenge trials with two to three of the most promising functional ingredients (alone and in combinations) will continue during 2019 in Norway, while the plan is to have at least one challenge trial with Caligus rogercresseyi in Chile. A co-infection trial with C. rogercresseyi and one bacterial species is also in planning and we expect that WP2 will benefit from knowledge gained in this trial.

**Molecular Techniques**

In addition to screening host responses by using microarray technology, the use of RNA sequencing (genome-wide method for gene expression profiling) of lice samples is expected to reveal effects of diet on the parasite, and in this way further contribute to the development of functional feeds. Microarray chips have not been developed for C. rogercresseyi and L. salmonis and RNA sequencing is thus the most suitable tool to study responses in the parasite at genome wide level.

One RNASEq publication of lice responses to the anti-attachment diet is in its final stage while transcriptome sequencing of field lice samples is currently taking place at the Norwegian Sequencing Center in Oslo.

Partners at IPMC/GAPP2 co-infection grant have been developing multiplex GeXP sets of 20–25 genes to screen host responses; there are currently three sets called anti-viral, general plex and anti-bacterial. The GeXP instrument will be relocated from Norway to Chile during 2019, and we anticipate higher use of the GeXP approach for medium-throughput profiling of host responses to diets and lice infestation in the nearest future.

**Immune pathways associated with sea lice infection and effect of anti-attachment**

The array of endogenous, host-mediated protective mechanisms against lice is not yet fully understood. Effectors of immune responses that belong to Type 1/Th1 guided pathways have been proposed as main contributors to reduction of lice in salmonid hosts. Follow up work in this area assigned protective roles to specific immune pathways and genes; WP2 publications showed that highly susceptible Atlantic salmon host can successfully be boosted by functional feeds to repel or inhibit attachment and reduce lice numbers during the course of infestation. Nutrigenomic signatures of immunoprotection by glucosinolates revealed protective role for a number of anti-viral factors in salmon skin, and detailed interrogation of these genes and pathways has continued in WP2 and associated IPMC/GAPP2 project. The effect of several tested products of microbial origin is also currently being analysed by microarrays at IPMC/GAPP2. In Norway, we will continue to use ELISA based methods to screen immune factors expressed in salmon mucus (two complement factors).
We have also proposed that iron regulation, the so-called nutritional immunity hypothesis, plays a role in the outcome of infection, and some of our latest findings further support this hypothesis. We plan to test this hypothesis in a trial with the most promising phytogenic compounds that were able to modulate iron pathways in our SHK cell culture system.

We will focus on finalizing analysis and summarizing all achieved results in the number of publications by the end of the center in 2019.

WP3: Immunomodulation of the host
Principal Investigator: Øystein Evensen, NMBU

WP3 addresses Immunomodulation of the host. The concept is that sea lice releases a series of secretory/excretory products (SEP) that have local and systemic effects via their salivary glands to prevent inflammatory responses to infection. To better understand and design therapeutic intervention that can alleviate or counteract the effects of the secretory products, the underlying mechanisms of inflammation and anti-inflammatory processes must be understood. Further to this, immunoprophylactic measures have been studied over the last year with a focus on vaccines or vaccine formulations that reduce infection load after experimental challenge.

In vivo fish (Atlantic salmon) challenge with copepodid
Sea lice copepodids modulate the immune response of the host after attachment, likely aiming at inhibiting the host’s immune responses and inflammatory environment locally and systemically to infection, which will facilitate lice attachment and preserve tissue integrity. The impact is systemic and to understand to what extent these lice-induced responses also impact on the anti-viral responses, peripheral immune cells (monocytes) of lice-infected fish were isolated from blood, propagated in culture, and thereafter infected with salmon pancreas disease virus (SAV3). The replication of virus and cellular responses to infection was measured over 6 days post infection. Macrophages from lice-infected fish had significantly higher levels of virus replication compared to macrophages from fish that had not been infected with lice (Fig. 3.1). These findings indicate that the anti-inflammatory lice-induced responses impact on the ability of the fish to control virus infections.
Figure 3.1: Relative levels of the E2 gene of SAV3 measured by real-time PCR at 2, 4 and 6 days post virus infection. Significant differences are seen at 2 and 4 days post infection.

Vaccination and challenge experiment
Vaccination and challenge experiments are carried out as common garden experiments where multiple vaccine candidates are injected into different groups of fish that are tagged and kept in the same tank. Non-vaccinated controls are also present in these tanks. The infection efficiency depends on the viability of the copepodids, time allowed for the copepodids to attach, temperature, and also the fraction of susceptible fish in the tank. When non-treated fish (controls) are kept alone in two parallel tanks (P1 and P2, Fig 3.2) and infected with 30 copepodids, the infection efficiency is typically around 65–70%, with some variation between fish. When non-treated control fish are kept together with treated fish (treatment that made them resistant to infection) at a ratio of 1:5, the average infection efficiency dropped to 31–38% in three different tanks (Fig. 3.3).

Figure 3.2: Control fish in 2 parallel tanks, infected with 30 copepodids/fish for 30 minutes, stagnant water (oxygenated). Challenge at time point 1 (T1).

Figure 3.3: Control fish in 3 parallel (tanks P1–P3), infected with 30 copepodids/fish for 30 minutes, stagnant water (oxygenated). Ratio of susceptible to resistant fish was 1:5 with a lower infection efficiency. Challenge at time point 2 (T2).
Vaccination and challenge studies – recombinant proteins

Vaccine candidate identification is a needle in the haystack exercise. Different recombinant antigens have been tested and two peroxidases gave a marked reduction in lice numbers upon initial vaccination and challenge testing. These enzymes have been subject to more detailed investigation and preliminary in situ hybridization has shown expression in ovaries and egg strings.

**Figure 3.4:** Positive (red color) reaction in ovaries (left) and egg strings (right).

Following vaccination and challenge the reduction in lice numbers was highest for the chalimus stage and pre-adult females, 57 and 22%, respectively.

**Figure 3.5:** Reduction of lice numbers in vaccinated fish relative to controls (set at 100%) for chalimus, and pre-adults males.
WP4: Molecular parasitology – the basis for novel treatment methods

Principal Investigator: Rune Male, UiB

The research in WP4 covers three areas of salmon lice Biology; Copepodid biology, reproduction & endo and exocrine systems. The research stretches over different thematic subjects such as signal transduction, gene expression and regulation, excretory products, energy metabolism, molting regulation and enzymes. From a more descriptive focus, including establishment of general resources and methods, research in WP4 has changed to a more functional direction. However, method development like improved vaccination procedures are still important. The research in WP4 have revealed several biological mechanisms that may represent bottlenecks in the live cycle of the parasite and have potential for use in fighting the parasite. Development of a vaccine receives special attention. This is a high-risk project with potential extremely high gain even if only partly successful and is therefore an activity that need to be continued. Vaccine development is highly resource demanding on both scientific competence and specialized aquaria and lab facilities, and the actual number of skilled hands needed to perform such experiments strongly argues for that continuation of vaccine trials will require a well-organized structure after the end of the SLRC as SFI.

Molting: biology and endocrine regulation
Arthropods represent by far the most species-rich and diverse group of animals on earth. They all have one thing in common; a robust chitin-based exoskeleton that can be exchanged and rebuilt as the organism grows. This process of molting may represent a bottleneck in the life of the animal and represent a possible target for weakening the parasite. The molting process is complex, energy demanding and leaves individual animals with reduced protection for a short period of time. The process of building and degradation of the chitin exoskeleton, and the regulation of these processes has been under continued study also in 2018.

Validation of computational network data
Network analyses of RNA expression data of genes was done in WP5 to identify genes associated with molting, and thereafter used as input for experimental testing. Genes with a central role in these networks were chosen for RNAi knock down in nauplius or in pre-adult 2 lice. By that, their role in molting should be investigated and it should be tested if network analysis can help to find important genes. Experimental knock down of one particular gene resulted in loss of lice from fish as chalimus when the knock down was performed in the nauplius stage, as well as no reproduction when the knocked down was done in pre-adult 2 lice, showing that this gene has an essential role in survival. Network analysis was also done with an RNA expression dataset regarding host parasite interaction. In addition, here some genes in central positions were chosen for knock down in pre-adult lice. Two genes showed no or reduced fecundity respectively.
**Enzymes**

Chitin synthesis and degradation processes are conserved and thus similar in all arthropods. A series of enzymes are responsible for the steps in synthesis and degradation of chitin has been studied in the salmon louse (Hardardottir et al. 2018). Furthermore, a sensitive assay for chemicals that block chitin synthesis has been established. The assay confirmed the action of several believed chitin synthesis inhibitors and determined their individual potency as molt inhibition down in the low Nano molar range equal to 1 gram in 1000 m$^3$ water.

**Regulation**

Steroid hormones are important regulatory molecules in *L. salmonis* and are also involved in molting. Biosynthesis of the steroid hormone involves a series of enzymes where several are coded by the Halloween genes that are now shown to be expressed in the intestines and in the gonads. Two steroid hormones seem important regulators in salmon lice as 20-hydroxyecdysone and ponasterone A were detected in lice by LC/MS analysis (Sandlund et al 2018).

Ecdysteroid treatments of nauplius larvae caused complete arrest during molting, in the transfer from nauplius II to copepodid stage. The effect was highly dependent of identity of hormone used. This observation and the data from RNAi knock down of Ecdyson receptor, argues for a hypothesis where molting is initiated by a dramatic drop in hormone concentration. This is in agreement with the mechanism in several insects. In salmon lice, ecdysone hormone treatment disrupts the expression of several regulatory factors (including HR3, HR4, E75, E74, aFTZ-F1, bFTZ-F1 and HR39) throughout the nauplius II stage.

**Figure 4.1:** Knockdown of FTZF1 isoform affect cuticle integrity and prevents molting. Pre-adult 1 males were injected with dsRNA and left to develop to adults. No adult males were observed at the end of the experiment. Lice **a** and **b** represent pre-adult 2 male individuals discovered in tank filters prior to adult molt and show abnormalities in the cuticle. Lice **c** is an image of a healthy pre-adult 2 male.
The Ecdyson receptor is positioned on the top of a cascade of regulators, each with varying direct protein-protein contacts to other regulators, both in time and place. The expression profiles of the putative ecdysone inducible factors (named HR3, HR4, E74, E75 and FTZ-F1) have been determined for pre-adult 1 and nauplius II stage and reveal similar and distinct patterns in both stages. Two of them (HR3 and HR4) show high expression at the start of the molt cycle, then drop rapidly and are at their lowest expression immediately prior to next molt. Several factors (aFTZ-F1, bFTZ-F1, E74 and E75) show an opposite pattern (to HR3 and HR4) with increased expression at mid-molt.

One of the characterized regulators, named FTZ-F1, has an isoform that following RNAi knock down caused developmental arrest in larvae. Repeated RNAi experiments on pre-adult 1 animals resulted in 100% mortality apparently due to molting complications as the animals displayed abnormalities in the cuticle (Figure 4.1). FTZ-F1 function is crucial for adult and larval molt, and as such possibly crucial to molting in all salmon louse stages.

Reproduction: germ cell differentiation and maturation
The Ecdyson receptor gene cascade is also involved in reproduction. RNAi knockdown of two of the studied gene regulators and nuclear receptors, that are putative members of the ecdysone regulatory cascade in in pre-adult 2 females, results in apparently normal ovaries but with abnormal oocyte stacking in the genital segment, and oocytes appear to die during maturation (Figure 4.2). Knockdown of the Ecdysone receptor reveals a similar phenotype and collectively these results suggest that ecdysone signaling is required for oocyte maturation.

Figure 4.2: Knockdown of two separate nuclear receptors in the ecdysone regulatory cascade affect oocyte maturation in similar ways. Pre-adult 2 females injected with dsRNA targeting two nuclear receptors resulted in similar phenotypes where a) oocytes die and display an abnormal stacking pattern. b) A similar section from a louse in the control group. The triangle highlights the cement gland, and the rectangle highlights stacked oocytes in the genital segment.

One of the main problems regarding salmon lice is their high reproductive capacity. An adult female can produce hundreds of eggs every few weeks which are stored in egg strings that are attached outside to the female until hatching. The egg strings stabilize and protect the delicate eggs from the outer surroundings. If one manages to destroy the egg string structure, this could prevent the reproduction of the lice. However, knowledge of the
molecular composition of the egg strings, necessary to specifically target them, is sparse. It was possible to identify several genes in the cement glands that appeared to be responsible for the production of the so-called cement that forms the egg strings. Analysis of the proteins in the cement using mass spectrometry confirmed the presence of the proteins encoded by these genes. A knockdown of these genes using RNA interference technology led to either clearly malformed egg strings or no egg strings at all. A phylogenetic analysis showed that similar genes and proteins are only present in a small, specific group of closely related copepods but not in other animals. This knowledge may help in the development of new drugs, specifically targeting the reproduction of salmon lice.

Figure 4.3: Dissection of the cement gland. The cement gland is marked with the red arrow.

**Immunomodulation and exocrine systems in sea lice; characterization and function at host infection**

Five salivary gland proteins with unknown function have been studied in addition to four astacins and one trypsin. The unknowns are short proteins, mostly with signal peptides that are expressed in the salivary gland only of salmon louse parasitic stages. Three are highly expressed at the time of attachment, while four are only/also highly expressed in pre-adult and adult stages. They have been fully sequenced and RNAi studies have been conducted. Three of these proteins have been knocked down in copepodids and infestation studies have indicated an immune modulatory role particularly for one of these proteins. This protein seems to dampen both the inflammatory and humoral immune response (Figure 4.4), however, the transcript level of T-cell and Non-specific cytotoxic cell marker genes were not affected. Two of the unknowns are only expressed in adults, where only one of those seem to be secreted. A recombinant protein has been made for this protein, and the immune response of LPS stimulated primary head kidney leukocytes have been modulated. Four highly similar astacins have been detected in the salivary gland, two expressed mainly in early stages while the other two seems to be more important in pre-adult and adult stages and is also expressed in a few other glands. Knock down of the two...
astacins in copepodids revealed a dampening response on the inflammatory response but no regulation of B-cell genes as IgM, IgT or IgD were detected. No immunomodulatory function of the trypsin was observed.

Rhabdovirus infections in salmon lice have also been studied. We developed a method to cure a cohort of lice for the two rhabdoviruses that are identified by the introduction of dsRNA. Three strains of lice have been established from a common origin, one with both viruses, one with only one of the two viruses and one that are virus free. Furthermore, we have infested fish with these strains to see if they influence survival and the reproductive capacity, and if they modulate the immune response of the host. No effect on survival and reproduction was seen, but some increase in inflammatory gene expression were seen in fish infested with rhabdovirus free lice. We have further analyzed the expression of salivary gland genes in the rhabdovirus free and infected lice strains, and found some increase in the transcript level of the trypsin. It is therefore uncertain if the decrease in inflammatory genes in response to rhabdovirus infected lice is a direct modulatory effect of secreted virions, or if virus replication is altering the level of louse salivary gland proteins.

**Figure 4.4:** Expression of interleukin 1 beta (IL1β), immunoglobulin (Ig) T and IgD in skin samples of salmon infested with control and knock-down (KD) lice. One unknown salivary gland gene was knocked down and a significant higher expression of the immune genes were detected, suggesting that this protein is involved in the dampening of the inflammatory and humoral immune response.

**Novel treatment targets – vaccine candidates**

In 2018, further work of characterizing genes and proteins related to iron and heme trafficking/storage in the salmon louse was continued. The work on the heme receptor was submitted to Scientific reports, and is now accepted for publication. The recombinant protein was produced, and a subsequent binding assay proved that the receptor binds heme in vitro.

The iron storage protein ferritin has been characterized in the salmon louse. Here, a RNAi gene knock down resulted in adult female lice that did not feed on blood, and that did not produce eggs (Figure 4.5). These results, together with the localization of the transcripts (in situ hybridization) and sequence analyses will be published in 2019.
Figure 4.5: Adult female louse phenotype after knocking down ferritin by RNAi. The control louse (A) has a blood-filled intestine seen as a red line stretching throughout the body, and a genital segment filled with developing eggs (oocytes). The ferritin knockdown louse (B) has a clear gut, and highly underdeveloped oocytes.

Vaccination and lice challenge experiment

An experiment including 11 vaccine groups was conducted. Vaccination was done with different lice antigens in the form of peptides, proteins, or lice extract. These were formulated in a water in oil adjuvant. Fish were ~80g at vaccination. A boost vaccination was given six weeks later. Fish were challenged with around 80 lice per fish approximately 2 months later, either in a common garden setup or for some groups in single fish tanks in addition. While termination of the experiment in the common tank should be at an early stage as chalimus and pre-adult 1 lice to avoid host switching, termination of fish from single tanks was done when lice were in the adult stage. The experiment was implemented at 12 degrees and sampling and counting of lice was done two weeks after infection in case of common garden setup, and 62 days after infection in single fish tanks. At sampling, fish weight, length and appearance were documented together with lice numbers of different stages (Figure 4.6). Fish growth was not significantly different between vaccine groups and controls (Figure 4.7 A). As lice numbers are dependent on fish size, lice density was calculated (Figure 4.7 B). There was no significant difference in density nor number of lice between any vaccine group and controls. We did not see any sub-lethal effect of the vaccines on lice development either (Figure 4.6).

Fig 4.6: Distribution of different lice stages at sampling time-point two weeks after infection in the common garden experiment (left panel). Ch= chalimus, p= preadult. Documentation of parameters measured at termination (right panel).
Fig 4.7: Fish growth after vaccination was similar in all vaccine groups (A). Lice density (B) was not significantly different in any vaccine group. Groups are defined A–N. Red underlayed are controls (A for all groups but H and I, which have L and M as controls respectively).

New medicines and strategies for parasite control
During 2018, several experiments were conducted in order to gain further knowledge about the RNAi machinery of *L. salmonis* as well as to clarify the possibilities of using RNAi as a treatment method. Advances were made in the blood feeding experiments, which have confirmed that the louse is able to ingest blood experimentally (Figure 4.8). The search for alternative delivery methods of dsRNA to the louse, in order to provoke a specific RNAi response has consequently been advanced and new experiments are ongoing and should produce relevant results during 2019.

During late 2018, a large double gene knockdown experiment was conducted, comprising more than 400 salmon lice, where several RNAi machinery candidate genes were tested. The ongoing molecular analysis of the numerous groups of lice has provided very relevant
information on the topic and will help shape the next planned experiments. In this experiment, the importance of candidate genes for the RNAi machinery was tested by selective gene knockdown of the candidate (via dsRNA micro-injection) followed by a second dsRNA micro-injection targeting a well-known louse gene. The differences observed in the relative expression of the second gene have given strong hints about the relevance of the candidate. During 2019, the relevant candidates identified will be further scrutinized and new candidates will be verified using this method.

Figure 4.8: An adult female louse is observed following the experimental ingestion of Atlantic salmon heparinized blood: the louse was placed in a droplet and actively ingested the solution. The red coloration in the gut (blood) was absent at the beginning of the experiment.

WP5: LiceBase

Principal Investigators: Michael Dondrup and Inge Jonassen, UiB

Over the last six years, LiceBase has been developed as a major resource for functional genomics of sea lice and related organisms. A particular focus has been on supporting RNA-interference experiments and gene-expression data. Integration of new genomes and LiceBase has also played an important role in improving the annotation of the draft genome of *L. salmonis*. Another important role that has formed over the years is to provide essential expertise and support in bioinformatics and data analysis of complex genomic data. It has always been our aim to contribute to the promise of advancing the basic understanding of sea lice biology from a computational point of view, but also promote a slightly different perspective on the organism as an interesting source of general knowledge about parasite evolution and value to general biology. This theoretical perspective is
our prime contribution to the project, in addition to providing the information systems, analyses and candidate genes for potential drug and vaccine targets that have we delivered according to the original plan.

**LiceBase Portal and Data management**

The LiceBase portal is a web application operated on our servers making heavy use of virtualization infrastructure at UiB; its convenient interface to the underlying genome sequences and annotation data and search functionality is implemented using free open source software.

The most important components are Drupal and Tripal as well as the genome browser GBrowse. Using Drupal and Tripal we implemented a LIMS system for annotation of RNA-interference experiments, linking experiments, genes and observed phenotypes after ablation of mRNA. The RNAi-LIMS has been operational and constantly been improved since 2014 and has been used to annotate RNAi experiments and meta-data from within the SLRC.

Implementation of a new and improved design (Fig. 5.1 A) of the website makes it more accessible and usable (see [https://licebase.org/node/936538](https://licebase.org/node/936538) for more information).

**GDPR compliance**

At LiceBase we are committed to protecting the users’ privacy and the security of personal data. The European Union’s General Data Protection Regulation (GDPR) has prompted us to review our policies. We have therefore updated our data privacy policy and terms or use to comply with the GDPR. The most important technical change was to implement an explicit opt-in policy for setting cookies and user tracking and to respect ‘do not track’ browser settings, in addition, there is now an explicit option to withdraw consent at any time (Fig. 5.1 A). These changes were effective since May 25, 2018. As a side effect, we observed an immediate drop in site visits and user sessions reported by Google analytics. Because law does not allow us to track users without consent, GDPR compliance renders user statistics incomparable and therefore tracking statistics are not included in this report. It is likely that we will discontinue user tracking in the future because of its very limited utility.
Figure 5.1: A) New design of licebase.org. The new layout is tidier, easier to navigate, and more in line with modern web-design. Options that allow users to manage their privacy settings are depicted at the top. Most recent images from public RNAi experiments are depicted on the right. B) Associated RNAi experiments are linked to their respective genes and transcripts.

Genome annotation and new organisms
Throughout the reporting period, we have strived to improve the genome annotation and its utility for users. We have therefore assigned speaking gene names to most of the *L. salmonis* genome, using an automatic annotation algorithm (see https://licebase.org/node/936717 for more information). Gene pages are now also linking to associated RNAi
experiments that used them (Fig 5.1 B). We have further integrated the genome of the Antarctic-endemic copepod *Tigriopus kingsejongensis* and added further annotation. By using Blast results, it is now possible to directly compare a free-living and a parasitic copepod genome (see https://licebase.org/node/923701 for more information).

**RNA-interference experiments and annotations**

Two workshops for entering RNAi experiments were held in 2018 in June and November to which all researchers working with or planning to work with RNAi experiments were invited. These workshops were largely successful by yielding ~150 more annotated experiments, which also included new phenotypes. By the end of the year 2018, the number of experiments in LiceBase had then risen to 410, of which 150 were publicly available. The intention is to run two more data-entry workshops during the last year of the center, to ensure maximal data coverage.

We then conducted an analysis of the distribution of phenotypes in LiceBase. Out of the 410 experiments, 395 were annotated with a proper Ensembl gene or transcript id. 87 experiments were missing any phenotypic annotation, 36 were pure control experiments, and 176 were annotated as ‘no visible phenotype’ or ‘no phenotype’. The remaining experiments were categorized into 23 top-level phenotypes, of which ‘female reproduction’ (47), ‘survival’ (11), and ‘developmental defect’ (8) were the most common ones. ‘female reproduction’ is further broken down into various subcategories, out of which ‘shorter egg strings’ is by far the most abundant one. This result can be explained by the dominant use of pre-adult to adult females for successful RNAi trials. When comparing the two different initial stages of RNAi trials (after removing pure controls), the rate of phenotypes is much higher in experiments involving pre-adult stages than in nauplii (25% vs. 6%, missing was counted as none). While part of this result could be explained by pre-tests of knock down efficacy that were not expected to result in a phenotypic alteration or not as thoroughly inspected as in adult stages, the result might still give an indication that a measurable change of phenotype is harder to induce and/or observe in larval stages than in adult females.

![Figure 5.2: distribution of different annotated observed phenotypes in RNAi experiments in LiceBase. Annotations are sorted by frequency.](image-url)
WP5 has taken the lead in the search for new candidate genes either for a specified function, or for identifying new knock down or vaccine candidates, and genes causing resistance. We have analyzed an increasing number of RNA-sequencing data of mRNA and miRNA, in total over 500 samples. Using network analysis of large published gene-expression time-series data and data from a large-scale host-parasite interaction study to predict important genes relevant for adaption of the louse to its host. These compiled candidates were then knocked-down in RNAi trials in WP4 and the list of knock-down candidates was found to be enriched for changes in phenotype in pre-adult females.

Heme is an essential co-factor and micronutrient for all aerobic life. WP5 has previously contributed to the discovery and characterization of a novel scavenger receptor (LsH-SCARB) that is possibly involved in the intestinal uptake of heme from a blood meal. During 2018, improvement of a 3D model and conducted docking experiments to further predict heme binding residues and identify potential binding modes of the ligand has been made. For further experimental validation by recombinant expression and in vitro binding of this important receptor, WP5 has established a collaboration with the research group Biorecognition at the Department of Biomedicine, UiB. The discovery of LsHSCARB as a heme receptor might also be relevant for biomedical research in the future through its potential orthologs in humans.

**Perpetual operation of LiceBase**

WP5 is dedicated to safeguarding the investments made in LiceBase and the valuable data it contains for the future, also after the termination of the center in 2019. LiceBase is an international deliverable within the Norwegian Elixir node, which will guarantee partial funding for the operation of LiceBase until at least 2021. In order to become a resource of excellent scientific value and in respect of the public funding for the service and the data contained, we will make all data in LiceBase open to the public by the end of the funding period.

**WP6: LiceLab**

**Principal Investigators Lars Are Hamre, UiB and Sussie Dalvin, IMR**

LiceLab provides state of the art infrastructure and expertise for the SLRC to study sea lice and host parasite interaction. The Lice lab facilities are situated at the University of Bergen, at the Institute of Marine Research, and at Cargill in Dirdal. These facilities have a unique capacity to study sea louse biology, to perform large scale efficacy assays and RNAi experiments as well as capacity to cultivate material for research and to maintain lice strains with specific properties. This is of vital importance to:

- obtain detailed knowledge of sea louse biology in order to identify points of attack
- efficiently evaluate new candidate medicines
• effectively screen vaccine candidate targets and evaluate test vaccines
• identify drug resistance mechanisms and establish tools to determine optimal use of medicines
• evaluate effects of non-medicinal method

![Figure 6.1: Salmon lice with a pigment mutation (LsSpotted lab strain)](image)

![Figure 6.2: Pigment cells in the salmon louse (168x magnification) are located below the epidermis and are clearly visible through the transparent cuticle.](image)

**Lice stains**
A total of nine sea louse strains were maintained in 2018, hereunder three sensitive salmon louse strains, one inbred strain and strains resistant to various medicines and/or multi-resistant strains. One new pigment mutant strain and one strain with a suspected pigment regulation defect were established. Material for in vitro experiments and RNA and DNA purification was produced and sampled for academic partners in Bergen and Oslo, serving about 35 researchers/PhDs/master students with material for ongoing research.

“Transparent” lice became a topic in media during fall 2018, reporting that extensive use of cleaner fish may have led to evolutionary adaptations towards a population of more transparent lice to avoid predation by cleaner fish. If so, one of the most important tools fish farmers have against lice may potentially lose its effect in the near future. A “transparent” strain of lice has been established to evaluate whether “transparency” has a genetic basis, or is controlled by environmental factors. This work is done in collaboration between WP6 and IMR.
A strain of pink salmon (*Oncorhynchus gorbuscha*) was established based on egg batches collected from a local river late fall 2017. This is the smallest and most abundant species of pacific salmon and they display a substantial resistance towards the salmon louse. The strain was established in order to study resistance mechanisms.

![Young pink salmon in the laboratory.](image-url)

Salmon louse viruses are present at a prevalence close to 100% in the lice populations along the Norwegian coast, and thus also in our laboratory strains. Considering their omnipresence, these viruses must be considered an integral part of the overall sea louse biology. As other collaborating research groups identify new viruses, our strains are screened to keep an overview of the status of the louse strains we work with. The interactions between the sea lice, their viruses and the fish host are assessed in collaboration with the ParaFishControl project. This allows us to assess whether the viruses may affect the outcome of other studies taking place in the Centre and improve our experimental control.

**Screening for vaccine targets and functional data.**

The salmon louse genome has been fully sequenced, but individual gene sequences often only contain little or no information about their biological role. Often further investigations are needed to obtain information about the function of a gene. In WP6, a method called RNA interference (RNAi) is used. RNAi is performed by introduction of double-stranded RNA into the salmon louse either by soaking or direct injection. RNAi works by temporal (2–40 days) removal of specific gene products. The condition of the animals...
after this treatment is inspected in live animals, and/or fin detail in animals that have been sectioned in thin slices, or by analysis of gene expression. Effects can range from changes in development, reproductive output, decreased digestion to behavioural change and mortality. Potential vaccine candidates should target proteins that have essential function for the louse. Because RNAi provides functional data, it is also used as a tool to evaluate such targets for vaccines. Two types of RNAi screens were carried out in the wet lab; I) RNAi in nauplius and II) RNAi in pre-adult and adults. Evaluation of RNAi screens from 2018 is on-going and results on specific genes will be reported from WP4. An overview of all experiment and results obtained is summarized in the table below.

<table>
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<th>Year</th>
<th>Method</th>
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<th>Total gene targets</th>
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<td>Pre-adult</td>
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<tr>
<td></td>
<td>Pre-adult</td>
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<td>254</td>
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Table 1: RNAi experiments performed at the SLRC. Total RNAi experiments reflect the total number of fragments injected or incubated. Total gene targets: this number shows how many different genes have been tested, i.e. total numbers minus controls and replicated experiments.

Vaccine trials. To follow up on successful RNAi experiments one vaccine trial with 11 targets was performed in 2017–2018 in a common garden set-up, but none provides significant protection against salmon lice infection.

Two new vaccine trials were initiated in 2018 testing a total of seven targets with termination spring 2019. Both trials are set-up with vaccine groups in separate replicate tanks.
At CARGILL facilities in Dirdal reconstruction of the tanks used for maintenance of host fish took place at the beginning of 2018. As described in the previous report, these tanks were moved outside of the Sea Lice Lab in 2017 and are now fitted with equipment that enables us to control water temperature and accelerate lice reproductive output according to our needs. Ability to increase water temperature allows for a more predictable and highly efficient production of egg strings, and consequently more stable production of large quantities of infective copepodids for In Vivo trials.

ASSOCIATED PROJECTS

New projects applied for are linked to the SLRC as associated projects. These projects are not a formal part of the defined work within the consortium, and some of the projects have partners from the centre, others have both the SLRC and other external partners. As the SLRC is going towards and end as a SFI in 2019, new projects and funding are important for the researchers in the centre. As an example, SLRC researchers have recently discovered the presence of orthologs of the major vault protein in the salmon louse. Vaults are large ribonucleoprotein complexes linked to multi-drug resistance and stress response that were previously not known to exist in arthropods. A collaboration with the Rome Lab at UCLA is established to study sea lice vaults, their function and potential utility for vaccine development. The project is funded by the Research Council of Norway and is expected to start in September 2019.

The table shows a broad variety in sources of funding:

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<td>9 363 610</td>
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Three of the associated projects:

Temperature and salmon louse development – Templus
Sussie Dalvin and Lars Hamre
Funded by FHF

Temperature and salmon louse development was studied at temperatures ranging from 3 to 24°C in the Templus project in collaboration with WP6 in the SLRC, where WP6 contributed in planning, data analysis and model development. A model describing the development (embryonic, planktonic and post infection growth) of lice in the temperature interval between 3 and 21°C was developed (manuscript submitted). The model is already frequently used in the experimental work carried out in LiceLab.

Post infection development of the salmon louse at 10°C for males (blue diamonds) and females (red squares). Y axis show the mean number of molts (MnM) undertaken by a batch of either males or females developing at 10°C as a function of days post infection. MnM=1.00 means that all lice have undertaken 1 molt while on the fish (all are chalimus 1). MnM=1.50 means that 50% of the population is chalimus 2 and so on. Population inter-molt phases (horizontal lines) and the phases where the population is molting from one stage to another (skewed lines) are easily identified and all together depict the development pattern of male and female *L. salmonis*.

Salmon louse sensitivity to freshwater and warm water project
Melanie Andrews and Tor Einar Horsberg
Funded by FHF

The usage of non-chemical treatment methods, such as fresh- and warm water bathing, to combat the salmon louse has increased from 176 reported treatments in 2014 to 1174 reported treatments in 2016 (Norwegian Food Safety Authorities, Prescription database,
With the increased use of these methods, there is a chance that tolerant individuals are selected and the population sensitivity shifts towards increased tolerance. It is today difficult to say if such a development has already started, if it is likely to become a problem in the near future, or if it is likely to ever become a problem.

Without standardized and validated bioassay methods, a future shift in tolerance levels will be difficult to demonstrate. Bioassays are routinely conducted throughout the production cycle to monitor the sensitivity of salmon lice populations to commonly used treatment compounds. If a decrease in treatment efficacy is identified, changes are made to the treatment plan; these include switching to a different treatment option and strategy. Bioassays are useful tools to monitor sensitivity towards treatments and without such tools changes in sensitivity, due to overuse of treatments, will not be detected and tolerance can be established in the population. By developing such a bioassay technique and robustly testing it, we aim to provide such a technique so that the industry is capable of testing on site the tolerance prior to treatment.

This project aims to increase our understanding of the effect that freshwater bathing has on the salmon louse, allowing the industry to prioritize treatments in order to obtain the best results. This part of the project builds onto our recently completed research, which resulted in the development of a bioassay method to determine the freshwater tolerance of different life stages of the salmon louse. Using the bioassay method we tested four geographically separate populations of salmon lice, we found that there were quite large population differences in tolerance to lower salinity levels in the copepodid stage, but less so on the pre-adult II stage. Our results indicated that the pre-adult II stage tolerated much lower salinity levels than we initially thought. This current project entails identifying and collecting salmon louse populations from southern, mid, and northern Norway over a 2-year period to determine whether there are population tolerance differences. This includes targeting populations in regions of consistently high or low salinity levels. Using egg strings collected from the selected sites, we rear parasites in the laboratory, which are then used to conduct freshwater treatment bioassays on the copepodid and pre-adult II salmon lice. On populations displaying different sensitivities, molecular work (RNAseq,
qPCR, sequencing of candidate genes) will be conducted to try to identify molecular markers suitable for in vitro tests for freshwater tolerance. In addition, the time-scale of changes in expression of affected genes will be studied.

A second, but equally important aim of the project is to determine the efficacy of warm water treatment on the removal of salmon lice. This is a treatment that is rapidly gaining in popularity as it is viewed as more environmentally friendly than chemical treatments. The treatment entails flushing Atlantic salmon with heated seawater for short periods, in order to dislodge salmon lice from the fish host. Unfortunately, not much work has been conducted on the effect that this treatment has on the salmon lice, although as for salinity tolerance, earlier work in the SLRC has demonstrated genetic variation in thermal tolerance (Ljungfeldt et al., 2017). We have already conducted a few trial experiments to start establishing bioassay methods to test the efficacy of this treatment on the different salmon lice life stages. Using the same populations of salmon lice collected for the freshwater tolerance research, we aim to continue development of a validated bioassay which may be used for routine checks. In addition, we aim to conduct the same molecular tests as described for freshwater treatments to identify affected genes suitable for being used as molecular markers in in vitro assays.

These two treatment methods, freshwater bathing and warm water treatment, are in the forefront of the battle against the salmon lice. This project aims to improve our overall knowledge of the treatments in order to preserve treatment efficacy, thus extending the lifespan of both treatments.

Deltamethrin resistance in the salmon louse Lepeophtheirus salmonis
Marit Bakke
Funded by NFR

The aim of this project is to describe how salmon lice (Lepeophtheirus salmonis) can protect themselves from the antiparasitic drug deltamethrin (DMT), i.e. the mechanism(s) behind resistance. Results obtained so far indicates a completely new resistance mechanism that has never been described in any species. Furthermore, the obtained knowledge on DMT-resistant salmon lice does not comply with the normal view on the effects of DMT. It has been shown that DMT resistance in the salmon louse is predominantly maternally inherited. This phenomenon was described by crossing females from a resistant salmon louse strain with males from a sensitive (not resistant) strain, and vice versa, and the DMT tolerance in the second generation of descendants was assessed. This was confirmed by results published earlier this year. Genes that are only passed on from the mother are found in the mitochondria, which are the cell components where energy production takes place. It was shown in our paper that there are differences in the mitochondrial gene sequences in resistant versus sensitive salmon lice. These changes lead to amino acid changes in the protein, which in turn may alter the function of the protein. Analysis of more salmon lice from geographically different locations will hopefully narrow down the list of genes in-
involved in resistance. How the energy production is linked to DMT resistance in the salmon louse was investigated by looking at how DMT affects apoptosis (controlled cell death), as alterations in the energy production may cause apoptosis. Recently published results show an effect of DMT exposure on apoptosis, and a difference between sensitive and resistant lice. At present, work is in progress to identify which proteins that are involved in the effect starting with DMT exposure and ending in apoptosis. Later in this project, we will look at DMT metabolism and how potential differences in metabolite compositions, or levels, may affect resistance. The results from this project will be useful to identify resistance on an individual level, with molecular markers. In addition, the obtained knowledge on the resistance mechanism and mode of action will be useful to avoid development of new medicinal compounds with overlapping modes of action. Such overlap will cause ineffective treatment against already DMT-resistant salmon lice.

INTERNATIONAL COOPERATION

The academic partners in the SLRC have all a strong interaction with foreign universities and research institutions. The key researchers in the SLRC are leading scientists within their filed of work and have a long experience in collaboration with research-groups and companies worldwide. They are attractive partners in international collaborating projects or at invited speakers at seminars. Well-established networks and collaborations have been further developed in 2018 through exchange of personnel and joint research projects. Young researchers in the SLRC have and continue to be encouraged to establish their own international network through participation in research projects and representation at international seminars and conferences.

For the industrial partners in the SLRC, major parts of their activities take place in UK, US/Canada and in Chile. With joint interests, it is a natural result that both the industrial partners and the research partners in the SLRC have a close collaboration with research institutions in these countries, as with Professor Sandra Bravo at the Austral University in Puerto Montt, Chile on resistance development in *Caligus rogercresseyi*. 
In 2018, the SLRC continued its collaboration with internationally recognized sea lice experts. In January, a workshop was held in Norway with visit by Mark Fast (Atlantic Veterinary College, University of Prince Edward Island, Canada), Simon Jones (Department of Fisheries and Oceans, Canada and University of Victoria) and Louise VG Jørgensen (University of Copenhagen, Denmark). During the workshop, current projects and plans were discussed between the SLRC and the visitors. Both senior and junior members of the laboratories joined the meeting.

In addition, collaboration between the SLRC and University of Copenhagen was strengthened through the stay of a senior researcher in Copenhagen (summer 2017–2018). The focus of this collaborative work was the immunological response to sea lice in rainbow trout. The collaboration resulted in a joint application for project funding to the RCN.

Moreover, within the ParaFishControl H2020 project, there has been collaboration between University of Copenhagen and the SLRC, where the in vitro action of salivary gland proteins have been tested. In addition, there has been collaboration with Instituto Nacional de Investigación y Tecnología Agraria y Alimentaria in Madrid, Spain, looking at the chemokine response against the salmon louse.
Mobility in 2018

- Visit from Researcher Marieke Verleih, Leibniz Institute for Farm Animal Biology, Germany, to UiB in winter/spring 2018
- Tinkara Vosel, Exchange student from University of Ljubljana, Slovenia visiting UiB in September and October 2018
- Hege Sørvåg Hauge, Heidi Kongshaug, Sussie Dalvin, Lars Hamre, Aina Øvergård and Ingunn Wergeland, UiB, have all visited University of Prince Edward Island during 2018.
- Marit J. Bakke visited the University of Gent in 2018 to learn methods for studying the activity of different complexes in the electron transport chains in mitochondria

Andreas Borchel

It all started with an email from a colleague I had met the year before at the International Congress of Invertebrate Reproduction and Development. She was going to be co-chairing a session at the Marine Evolution 2018 symposium in Strömstad in Sweden and maybe my research might fit in. The session’s topic would be “Sex in the oceans: from molecules to macroevolution”. As my work focuses on (molecular) reproductive biology of salmon lice, this fit quite well. As the rest of the conference program looked quite appealing as well, I participated at the conference in Strömstad from the 15th to the 17th of May, 2018. The conference was organized by the Centre for Marine Evolutionary Biology, celebrating their tenth year as a Swedish Centre of Excellence. While the main focus of the conference clearly lay on evolution, molecular processes were also a big topic, for example in the session “Epigenetic processes and non-genetic inheritance in marine species adaptation” or “Genomic discoveries from novel marine model organisms”. The session I participated in, offered fascinating insights into reproduction from a variety of species, ranging from sex-changing fish, through kelp, to marine diatoms. The conference also featured several social activities and possibilities to get in contact with each other, for example Swedish “fikas” after the keynote presentations or a “walk and talk”, an organized tour in the surroundings of the conference hotel. However, the main social activity was a boat excursion to the Kosterhavet national park including a trip to the beautiful island Nordkoster with an amazing beach, where a specific snail species, known from several population genetic studies, lives. Overall, the conference was very interesting as it opened the eyes for a lot of research topics in the field of genomics and evolution.
COMMUNICATION OF THE SRLC RESEARCH

Communication of research and results are crucial for an SFI. Throughout 2018, researchers and industrial partners have presented the SLRC activities at a broad range of national and international meetings and conferences. At national level, industry, authorities, private and public organizations and society in general, are interested in sea lice research and news from the SLRC.

LiceLab and the facilities for experiments on sea lice are interesting to visit for existing and potential collaborative partners for the SLRC. A major task for the center is to explain about sea lice and the importance of its management and control. The SLRC has been an important contributor to the Norwegian documentary “Den fantastiske villaksen” which was shown at NRK in February/March 2018. Moreover, in August Reutes recorded a documentary on salmon louse.

The SeaLice 2018 conference was hosted in the town of Punta Arenas, located in the Strait of Magellan in the southern part of Chile. The conference took place in the beautiful Dreams Casino Hotel along the water’s edge from the 4th to 8th of November. There were about 350 attendees from more than 10 countries. Although a scientific conference, the majority of the attendees were from the salmon farming industry, while roughly a
third of attendees were researchers. The conference talks were divided into six sessions: sea lice biology, epidemiology and modelling, treatment and control, pharmacology, genetics and molecular biology, and wild fish interaction. 9 scientists represented the SLRC at the conference with posters or oral presentations. In addition, Professor Tor Einar Horsberg (WP1) was invited to give a presentation of the work and results from 7 years of research in the SLRC and the plans for the center’s future directions. The next Sea Lice conference will take place on the Faroe Islands in 2020 SLRC delegation at ISAAH 2018.

ISAAH 2018: Four researchers from the SLRC were visiting ISAAH 2018, the 8th International Symposium on Aquatic Animal Health, held in Charlottetown, Prince Edward Island, Canada. The conference had a wide scientific scope, and gathered Aquatic Animal Health Professionals from across the world, with an attendance around 350 participants. Diverse ranges of topics were covered in immunology, parasitology, bacteriology, virology and mycology related to both vertebrate and invertebrate farmed aquatic animals. Sea lice was also an important topic covered in three separate sessions. Talks on lice viruses, immunology, co-infections, temperature dependent development rates, lice prevention technologies, functional feed and sea lice management were given. The centre contributed with three talks and one poster.
Havbrukskonferansen 2018: Four researchers from the SLRC presented the recent research in the centre in April. The conference is a biannual arrangement by the RCN and FHF where the purpose is to gather researchers, industry and politicians to present and discuss relevant research. The theme for this year’s conference was “Havbruk i samfunnet”.

Summary of dissemination activities in 2018

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RECRUITMENT

The SLRC as a SFI is going to end in August 2019 and no new PhDs and Postdocs have been recruited to the centre in 2018. One PhD thesis was submitted during the year and 3 more are expected to finalize their PhD in 2019. PhDs in the centre are a part of the PhD programmes at UiB or NMBU, and have the opportunity to follow regular courses and seminars.

The centre is happy to see that both PhDs and Postdocs educated in the SLRC are attractive for industrial companies working with the sea lice challenge as well as for the academic institutions. Permanent positions offered to young SLRC personnel underline the quality of work made in the centre.

The CASL Summer School 2018 in Experimental methods in Sea Lice Research was arranged 18–22 June in Bergen. 14 master and PhD students from Canada and Norway participated at the course. The program included theory and methods for a selection of advanced molecular research methods applied on salmon lice. Lectures covered the theoretical background for methods used in the course, the live cycle of the salmon louse and selected topics from recent research on the parasite. Hands on lab work and demonstrations of methods were in focus. An excursion to the IMR experimental facilities in Matre was included in the course. One of the aims for the Summer School is to establish a valuable network for the future.
Joao Barbosa

As a PhD student in the Sea Lice Research Centre, I had the opportunity to attend the Bergen Summer Research School 2018 (BSRS 2018) as part of my educational curriculum. Roughly, one hundred PhD students from all over the world attended and enrolled in one of the six courses available. During ten days, students partook in lectures and plenary sessions with professors, researchers and policy makers. I was selected to attend the “Can the oceans contribute more to our food security?” course, led by Professor Øyvind Fiksen (UiB). At the core of this course was the most recent report submitted by SAPEA (Science Advice for Policy by European Academies) to the European Commission: “Food from the oceans. How can more food and biomass be obtained from the oceans in a way that does not deprive future generations of their benefits? High-Level Group of Scientific Advisors Scientific Opinion No. 3/2017”. Students from Greece, Cameroon, France, South Africa, the Netherlands, Namibia and Norway presented their research subjects ranging from the study of White Fish Storage Properties to the Benguela Current System. The diverse background of the students led to very lively lectures and discussions, as the dissimilar educational and cultural experiences produced different perspectives and approaches to the problem.

Among the invited lecturers, the highlights were the two lectures focusing on the SAPEA report by Dag L. Asknes (UiB), the lecture on the properties and uses of macro-algae by Arne Duinker (HI) and the talk on the alternative view of fisheries management by Jeppe Kolding (UiB). Students were also tasked with coming up with their own presentations on the sustainable means of producing more food from the oceans, using the input received from the first week of lectures. Subsequently, all the groups merged to create a final presentation for the last day of the course. Following another round of lectures summarizing the courses and presenting the 2019 BSRS, the students were given the opportunity to present their work to their peers. Our group designed an interactive presentation where the public voted live on three answers to the question “Can the oceans contribute more to our food security?” while three different presenters sequentially defended their point of view in front of the audience. Our presentation highlighted the cost vs benefit of three different plans of actions, raising awareness that the “solution” can hardly come without a cost, no matter what the option is. All in all, attending the BSRS 2018 was an enriching experience that increased my wakefulness regarding some of the issues we, as a society, will be facing to feed the growing human population while having to protect our resources and make sure they will still be available for future generations.
# ATTACHMENT TO THE REPORT

## Personnel Sea Lice Research Centre

### KEY RESEARCHERS

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<thead>
<tr>
<th>Name</th>
<th>Institution</th>
<th>Main Research Area</th>
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<tr>
<td>Frank Nilsen</td>
<td>UiB</td>
<td>WP1, WP4</td>
</tr>
<tr>
<td>Sussie Dalvin</td>
<td>IMR</td>
<td>WP4, WP6</td>
</tr>
<tr>
<td>Rune Male</td>
<td>UiB</td>
<td>WP4</td>
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<tr>
<td>Tor Einar Horsberg</td>
<td>NMBU</td>
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<td>Øystein Evensen</td>
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<td>Simon Wadsworth</td>
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<tr>
<td>Inge Jonassen</td>
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<td>Lars Hamre</td>
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<td>Christiane Eichner</td>
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<td>Michael Dondrup</td>
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<td>Kevin Glover</td>
<td>UiB</td>
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<tr>
<td>Stanko Skugor</td>
<td>EWOS</td>
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<tr>
<td>Sindre Grotmol</td>
<td>UiB</td>
<td>WP4, WP6</td>
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### VISITING RESEARCHERS

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<td>Marieke Verleih</td>
<td>Leibniz-Institute for Farm Animal Biology</td>
<td>German</td>
<td>22.02.–01.04.2018</td>
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<tr>
<td>Tinkara Vosel</td>
<td>University of Ljubljana</td>
<td>Slovenian</td>
<td>17.09.–26.10.2018</td>
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### POSTDOCTORAL RESEARCHERS WITH FINANCIAL SUPPORT FROM THE CENTRE BUDGET

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<td>Kiranpreet Kaur*</td>
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<td>01.01.17–01.08.19</td>
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<td>Melanie Andrews</td>
<td>South African</td>
<td>01.08.14–31.07.18</td>
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<td>Andreas Borcher</td>
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<td>Liv Sandlund</td>
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<td>Helle Holm</td>
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<td>Hetroneny Mweemba</td>
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<td>Koestan Gadan*</td>
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<td>Amr Gamil*</td>
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* Researchers working at Post doc. level
### POSTDOCTORAL RESEARCHERS WORKING ON PROJECTS IN SLRC WITH FINANCIAL SUPPORT FROM OTHER SOURCES

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<td>Celia Agusti-Ridaura*</td>
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<td>Anna Komisarczuk*</td>
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* Researchers working at Post doc. level

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<td>Nandhini Mohan</td>
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<td>WP2, WP3</td>
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**Administrative Personnel with Financial Support from the Centre Budget**

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<tr>
<td>Frank Nilsen</td>
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<td>01.09.11–</td>
<td>M</td>
<td>Centre Leader</td>
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<tr>
<td>Ingunn Wergeland</td>
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**Accounts**

**All Figures in 1000 NOK**

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<td>Other public financing*</td>
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<td><strong>Total</strong></td>
<td><strong>28 008</strong></td>
<td><strong>35 059</strong></td>
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<td>15 389</td>
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<td>Enterprise partners*</td>
<td>6 640</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>28 008</strong></td>
<td><strong>35 059</strong></td>
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*Given names for each group of partners.

The total activity for the SLRC in 2018 was 28,008 mill NOK compared to a budget of 35,059 mill NOK.
<table>
<thead>
<tr>
<th>No</th>
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</table>
| 1  | Anna Z. Komisarczuk, Heidi Kongshaug, Frank Nilsen  
| 2  | C Eichner, M Dondrup, F Nilsen  
| 3  | E Harasimczuk, AC Øvergård, S Grotmol, F Nilsen, S Dalvin  
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Identification and characterisation of the ecdysone biosynthetic genes neverland, disembodied and shade in the salmon louse (*Lepeophtheirus salmonis*) (Copepoda, Caligidae)  
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Recent advances in salmon louse research. Bull. Eur. Ass. Fish Pathol., 38(3) 2018  
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https://doi.org/10.1186/s13071-018-3151-7


2017

<table>
<thead>
<tr>
<th>No</th>
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<th>Partner</th>
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| 1  | **AC Øvergård, C Eichner, F Nilsen, S Dalvin**  
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Cell Stress and Chaperones, DOI 10.1007/s12192-017-0830-9, June 2017  
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Migration of Atlantic salmon post-smolts in a fjord with a high infestation pressure of salmon lice. Marine Ecology Progress Series

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3  Aaen SM and Horsberg TE

A screening of multiple classes of pharmaceutical compounds for effect on preadult salmon lice Lepeophtheirus salmonis

Journal of Fish Diseases, 2016 Apr 1. doi: 10.1111/jfd.12463

www.ncbi.nlm.nih.gov/pubmed/27037538

4  Kaur K, Jansen PA, Aspehaug VT and Horsberg TE


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5  Jansen PA, Grøntvedt RN, Tarpai A, Helgesen KO, Horsberg TE

Surveillance of the Sensitivity towards Antiparasitic Bath-Treatments in the Salmon Louse (Lepeophtheirus salmonis).


journals.plos.org/plosone/article?id=10.1371/journal.pone.0149006

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onlinelibrary.wiley.com/doi/10.1002/jmor.20611/full

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10  Skugor S, Holm H, Bjelland AK, Pino J, Evensen Ø, Krasnov A, Wadsworth S

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Disruption of host-seeking behaviour by the salmon louse, Lepeophtheirus salmonis, using botanically derived repellents.


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12 Helle Holm, Nina Santi, Sissel Kjøglum, Nebojsa Perisic, Stanko Skugor, Øystein Evensen Difference in skin immune responses to infection with salmon louse (Lepeophtheirus salmonis) in Atlantic salmon (Salmo salar L) of families selected for resistance and susceptibility Fish & Shellfish Immunology www.sciencedirect.com/science/article/pii/S1050464814004124

13 Liv Sandlund, Frank Nilsen, Rune Male, Sindre Grotmol, Heidi Kongshaug, Sussie Dalvin Molecular characterisation of the salmon louse, Lepeophtheirus salmonis salmonis (Krøyer, 1837), ecdysone receptor with emphasis on functional studies of female reproduction International Journal for Parasitology www.sciencedirect.com/science/article/pii/S0020751914002707#
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Emamectin benzoate and substance EX prophylactic evaluation against salmon louse infestation of sea-ranched Atlantic salmon smolts.
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| 1 | Mennerat, A., Hamre, L., Ebert, D., Nilsen, F., Davidova, M. and Skorping, A.  
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| 5 | Skern-Mauritzen, R., Malde, K., Besnier, F., Nilsen, F., Jonassen, I., Reinhardt, R., Koop, B., Dalvin, S., Mæhle, S., Kongshaug, H., Glover, K.  
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*Journal of Natural History*, online Nov 2012 | IMR |
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| 7 | Horsberg, T.E.  
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*Curr Pharm Biotechno* 2012, 13, 1095-1102. | NVH |

### 2011

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| 1 | Nilsen, F.  
Sea Lice Control  